CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
FORMALDEHYDE

Relevant studies are also found in Tolerance #50673:
formulated product "Glycoserve LAD"

Chemical Code # 000295, Tolerance # 01032
SB 950 # 064

Original date: 10/7/87
Revisions: 4/08/96, Jan. 2, 1997

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, inadequate study, possible adverse effect indicated[1]
Chronic toxicity, dog:	Data gap, no study on file[1]
Oncogenicity, rat:	Data gap, inadequate study, possible adverse effect indicated[1]
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	Data gap, inadequate study, possible adverse effect indicated[2]
Teratogenicity, mice:	Data gap, inadequate study, no adverse effect indicated
Teratogenicity, rat:	Data gap, inadequate study, no adverse effect indicated
Gene mutation:	No data gap, possible adverse effect
Chromosomal effects:	No data gap, possible adverse effect
DNA damage:	No data gap, possible adverse effect
Neurotoxicity:	Not required at this time

[1] Additional information is being requested which will allow reconsideration of data gap status for these study types, based on existing studies.

[2] There is no FIFRA-guideline style reproduction study. The "possible adverse effect" reflects information from a specialized study (see below).

Note, Toxicology one-liners are attached

In the one-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

Original Summary prepared by D. Shimer, 10/7/87.
Updated by: C. Aldous and J. Gee on 4/08/96, and by Aldous on Jan. 2, 1997.

The present summary includes all relevant records on file with the DPR Library as of Jan. 2, 1997. This includes all records up to 151312 (in Document No. 1032-054).

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

NOTE: These pages contain summaries only. Individual worksheets may identify additional effects.

ANALYSIS OF CHRONIC AND ONCOGENICITY DATA ACCEPTABILITY STATUS

The one-liners below indicate no "acceptable" chronic studies for any one species, and no "acceptable" rat oncogenicity study. The mouse oncogenicity data gap is filled by the 1981 Battelle Columbus study conducted for CIIT. The corresponding Battelle study in rats was classified by DPR as unacceptable due to failure to provide histological examinations for a full complement of tissues in intermediate dose groups. This is important, because the high dose level in that study exceeded the MTD.

A meaningful study or series of studies to fill a data requirement should (1) verify that intended dose levels were in fact administered, (2) clearly identify the characteristic findings at toxic level(s), (3) establish NOEL's or provide a clear dose-response curve. The next few pages provide an assortment of formaldehyde studies in various species, with dosing regimens of various durations, employing several routes of exposure. No single study is classified as individually "upgradeable", however several of these studies combined have the potential of addressing most of the key issues above. These main issues are presented one at a time, as follows:

Dose level verification: The 1981 rat CIIT inhalation study (Pavkov et al., Record No. 138989) utilized a stable source material (paraformaldehyde) to generate formaldehyde atmospheres. These atmospheres were adequately monitored. The two other major rat long-term studies (Til et al., 1989; and Tobe et al., 1989) also used paraformaldehyde as starting material, but both of the latter studies used drinking water as a dosing route (for formaldehyde derived from paraformaldehyde dissolved into the water), and neither reported on the stability of the drinking water solutions over the time frames utilized (4 to 7 days at room temperature). **A retrospective formaldehyde analysis of drinking water solutions derived from paraformaldehyde is essential to improve the utility of these studies.** A published report from one other relevant study (Rusch et al., 1983 Bio/dynamics 26-wk study in 3 species) utilized a different starting material [a 5% formaldehyde solution with comparatively low methanol levels (0.03%)]: that report indicated that chamber formaldehyde levels were regularly examined and found to have remained within specifications during the course of the study. Except for the information requested about drinking water stability of paraformaldehyde-derived formaldehyde, no other data about analysis of formaldehyde administered is requested at this time.

Identification of effects at toxic dose levels: The primary rat combined study (CIIT study of 1981) clearly identified a dose-related response in nasal turbinate epithelial changes. Findings such as squamous cell metaplasia were seen as low as 2 ppm (lowest dose tested). This study was found

unacceptable, primarily due to failure to systematically examine intermediate dose groups histologically. Aside from the toxicity to the nasal epithelium, several possible treatment relationships were noted in the review at the high dose level of 15 ppm. One finding noted at that level, but was not evaluated at lower dose levels: bone marrow hypercellularity or hyperplasia (beginning at 12 months, both sexes). The observation that iv administration of formaldehyde led to some sequestering in RBC's (see the 1965 study by Malorny et al. (Document No. 1032-029, Record No. 133142, toward the end of this Summary) suggests that comparatively high exposure of these cells could lead to increased RBC damage and turnover. Nevertheless, hematology data in the CIIT rat and mouse combined studies did not correlate with significant increases in blood cell turnover. This suggests that effects on hematology are likely to be far less important in hazard assessment compared to well-substantiated effects in the upper respiratory system. A consistent feature of the long-term studies below is that the major toxicity is found at the points of entry into the body (upper respiratory system in inhalation studies; forestomach and glandular stomach in rat drinking water studies). Comparative studies in monkeys and rodents (see two 1-liners by Monticello et al., both under Record No. 139033 in the "Oncogenicity, Rat" section of this Summary) suggest that the monkey is somewhat more sensitive than the rat to damage to the respiratory epithelium. These studies also indicate that the range of epithelial surfaces affected in monkeys extends to the nasopharynx. The species differences were interpreted to have arisen largely because the monkey (like man) is a mouth-breather during times of high oxygen demand. Studies such as the latter one are of potential value in "bridging" to human risk, since human airway anatomy and mouth-breathing capacity more closely resemble that of the monkey than that of the rat. It is the opinion of this reviewer that the collection of studies below (chronic and shorter duration, in various species) adequately address the issue of target organ toxicity. **Upon submission of the requested data from the last paragraph, the rat oncogenicity data requirement, and the rat and non-rodent chronic study data gaps should be considered filled.** Aldous, 3/26/96.

The establishment of a NOEL: It has been noted that the 1981 CIIT rat chronic/oncogenicity study did not identify a NOEL for nasal epithelial toxicity. There is nevertheless a clear dose-response over the range tested (2 to 15 ppm). The 6-month inhalation study by Rusch et al. (Record No. 139034) indicated that a NOEL under such conditions was 1 ppm for rats, and perhaps just below that level for cynomolgus monkeys. Additional studies, such as the cited 6-week comparative studies of rats and rhesus monkeys by Monticello et al., offer some means of bridging to man. Also, human exposures with 8 hr TWA's over 2 ppm are evidently not uncommon [see Document No. 1032-042, Record No. 139036; Blair et al., "Mortality among industrial workers exposed to formaldehyde", JNCI 76:1071-1084 (1986)], so that human epidemiological studies would be expected to identify characteristic chronic toxicity. The latter was a large historical cohort study, and was negative. Some other worker exposure studies suggest a formaldehyde tumor effect (typically of upper respiratory system epithelial cell tumors: see one-liners at the end of this Summary under "HUMAN EPIDEMIOLOGICAL STUDIES"). U.S. EPA has elected to use rat nasal tumor data to perform their risk assessments, in recognition of the "limited" evidence of similar human respiratory tumor effects at exposure levels within the lower range of the 1981 CIIT rat inhalation study. Aldous, 3/26/96.

COMBINED, RAT

1032-041 138989 Pavkov, K.L., et al., "A chronic inhalation toxicology study in rats and mice exposed to formaldehyde", Battelle Columbus Laboratories (conducted for CIIT). Original report date: 9/18/81. Date of present submission: 12/31/81. **THIS IS THE REVIEW OF THE RAT DATA.**

Paraformaldehyde was used to supply formaldehyde to F344 rats in inhalation chambers. Rats were exposed for 6 hours/day (5 days/week) for 24 months. Exposure levels were 0, 2, 6, or 15 ppm, with 120/sex/group. Study design was to kill the following numbers/sex/group at scheduled intervals: 10 at 6 months, 10 at 12 months, 20 at 18 months, 60 at 24 months, and 10 at each of two post-exposure intervals (study months 27 and 30). No NOEL was found in the range tested. A minor feature was that all treated groups developed yellow stained hair. The most notable lesions were observed in nasal turbinates: all treatment groups underwent dose-related changes in the morphology of the respiratory epithelium from the normal cuboidal non-ciliated or pseudostratified ciliated morphology toward a stratified squamoid appearance. Squamous cell carcinomas were found in 2 rats (1/sex) at 6 ppm, and in 46 males and 52 females by 2-yr sacrifice: most of these rats died on study, increasing mortality in both sexes at 15 ppm by 18 months, and progressively throughout the rest of the study. These tumors and associated lesions are "**possible adverse effects**". Findings not related to these respiratory effects were premature appearance or degree of prominent anterior lens sutures in eyes of 15 ppm males, and bone marrow hyperplasia (which was unfortunately not examined at lower dose levels). This study is **unacceptable and not upgradeable**, either as a chronic study or as an oncogenicity study. The primary problem is that intermediate dose groups were not routinely examined histologically, even though it was clear that the high dose groups exceeded an MTD. Kishiyama and Aldous, 3/25/96.

1032-042 139028: Publication of 041 138989. Kerns, W., K.L. Pavkov, D. Donofrio, E.J. Gralla, and J.A. Swenberg. "Carcinogenicity of Formaldehyde in Rats and Mice after Long-Term Inhalation Exposure". Cancer Research 43:4382-4392. September 1983. (Kishiyama, 8/21/95).

1032-045 139060 Swenberg J.A. et al., "Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor", Cancer Research 40:3398-4302 (1980). This is a published interim report of 041 138989, above. (no DPR review of this publication)

1032-040 138975 Til, H.P., R.A. Woutersen, V.J. Feron, V.H.M. Hollanders, H.E. Falke and J.J. Clary, "Two-year drinking-water study of formaldehyde in rats", TNO-CIVO Toxicology and Nutrition Institute, The Netherlands, published in Food Chemical Toxicology 27 (2) 77-87, (1989). Paraformaldehyde prills, 95% purity (5% water), were dissolved in tap water and administered to 50 Cpb:WU; Wistar rats/sex/group for up to 24 months at average concentrations of about 0, 20, 260 or 1900 mg/l of formaldehyde, achieving estimated dose levels of 0, 1.2, 15 or 82 mg/kg/day for males and 0, 1.8, 21 or 109 mg/kg/day for females. Additional rats were designated for 12- and 18-mo interim sacrifices (10/sex/group/interval). Many parameters assessed in a standard "combined" study were evaluated, excepting ophthalmology. Apparent NOEL = 15 mg/kg/day (males), 21 mg/kg/day (females): [focal papillary epithelial hyperplasia in forestomach, which late in the study evolved to include focal hyperkeratosis and focal ulceration; chronic atrophic gastritis in the glandular stomach, accompanied in the latter part of the study by glandular hyperplasia and focal ulceration; papillary necrosis of kidneys: all of the above were characteristic of both sexes]. The high dose caused marked body weight decrements. Marked reduction in water intake was a probable factor in body weight effects, and may have been a major contributor to kidney pathology. This is a potentially useful study: (1) It suggests that the focus of toxicity for formaldehyde solutions is at the point where high concentrations gain entry into the systemic circulation, here leading to preferential damage to forestomach and glandular stomach mucosal surfaces. (2) This study provides very little evidence that circulating formaldehyde reaches other tissues in sufficient quantities to elicit target organ toxicity. (3). Treatment achieved a full MTD without being excessively toxic. A serious limitation of this study was lack of analysis of dosing material to confirm stability, homogeneity and content. Since the dosing solutions contained formaldehyde

without a stabilizer, it is quite uncertain what the mean formaldehyde dose levels were, and how much of polymerization products, formic acid, or other degradates were ingested. A retrospective analysis of dosing solutions as prepared in this study would improve the utility of this report. This study is **not acceptable as an independent combined study**. It is also not upgradeable. Several weaknesses of this report reflect limitations of a publication format: no individual data (body weight, food consumption, water intake, hematology, clinical chemistry, urinalysis, clinical signs, or histopathology). There was no ophthalmology exam. **No adverse effects are indicated** (no oncogenic effects, relatively high NOEL's). Kishiyama and Aldous, 2/26/96.

CHRONIC, RAT

1032-040 138976 Tobe, M., K. Naito, and Y. Kurokawa, "Chronic toxicity study on formaldehyde administered orally to rats", Division of Toxicology, National Institute of Hygienic Sciences, Tokyo, Japan. Published in Toxicology 56:79-86 (1989). Twenty rats/sex/group received drinking water ad lib., containing 0, 0.02%, 0.10%, or 0.50% formaldehyde (derived from paraformaldehyde). Of these, 6/sex/group were designated for interim sacrifices at 12 and 18 months. NOEL = 0.02% (limited forestomach hyperkeratosis). Findings at 0.50% included forestomach lesions such as squamous cell hyperplasia, hyperkeratosis, basal cell hyperplasia, erosions/ulcers, and submucosal cell infiltration. Glandular stomach was less affected, however glandular hyperplasia, erosions/ulcers, and submucosal cell infiltration were noted. This dose led also to marked decrements in water intake, body weight decrements, and premature mortality (there were no survivors at 0.50% for 2 years). This study is **not acceptable, and not upgradeable**: (1) there were too few animals allocated for a study having 2 interim sacrifices, (2) a number of required tissues were not examined microscopically, and (3) one of the 3 dose levels exceeded the MTD, based on excessive mortality. Given that there is another drinking water route study which is more serviceable (e.g. Til et al., 1989, in this volume), no more information need be submitted at present relating to this study. Kishiyama and Aldous, 4/08/96.

1032-006 3734 "Freedom of Information Summary - Human Safety - Rat Feeding Studies." (Armed Forces Food Science Establishment, Australia, 1977). Rats were fed formaldehyde-treated fish 5 days/week for 12 months. Report is a very brief summary, insufficient for independent evaluation. **Unacceptable, not upgradeable** (dose levels not justified, study of too short duration for tumor development, very limited histopathology). J. Remsen (Gee), 3/22/85.

CHRONIC, DOG

No study on file.

CHRONIC AND SUBCHRONIC, MULTIPLE SPECIES

1032-042 139033 Monticello, T.M., K.T. Morgan, J.I. Everitt, and J.A. Popp, "Effects of formaldehyde gas on the respiratory tract of rhesus monkeys: Pathology and cell proliferation", CIIT. Published in Am J Pathol 134:515-527 (1989). Groups of 3 young adult male rhesus monkeys were exposed to test atmospheres 6 hr/day, 5 days/wk, either (1) for 6 weeks to room air (control), (2) for 1 week, to 6 ppm formaldehyde, or (3) for 6 weeks, to 6 ppm formaldehyde. The formaldehyde was generated by heating

paraformaldehyde in the airstream. Primary study objectives were to evaluate histopathology and cell proliferation, particularly to respiratory structures. Histopathology was performed on multiple transverse sections of nasal airways, including turbinates and sinuses; as well as larynx, trachea, and lungs. Several other major organs were also examined microscopically. Cell proliferation was determined by histoautoradiography of selected tissues (the nasal sections, larynx, trachea, carina, lung, and duodenum), and was reported as labeling indices. Histopathologic change and cell proliferation induction were both most profoundly evident in the respiratory epithelium (as opposed to transitional or olfactory epithelium). In the 1-wk exposure group, changes were primarily evident in the more anterior regions of the nasal passages. By 6 weeks, anterior/posterior differences were less evident for both histopathology and for labeling indices. There were no evident changes in histopathology or labeling indices in lung or in duodenum. There were no visible histopathology alterations in other organs evaluated. This study offers some comparisons and contrasts with effects in rats (see also Record No. 139032). Both species responded to formaldehyde by alterations of respiratory epithelium from columnar ciliated morphology toward layered squamous cell appearance. Both showed increased cell proliferation indices parallel with the histopathology changes. The monkey was evidently the more sensitive species. Lesions were observed to progress further into the respiratory passages in monkeys than in rats. This is probably partly due to the fact that the monkey (as man) is capable of using mouth breathing in times of high oxygen demand (unlike rodents), therefore man does not allow the same level of "scrubbing" of respiratory irritants in the upper nasal epithelium. The overall structure of the respiratory passages in man is more similar to that of monkeys than that of rats. For these reasons, the monkey appears to be a better surrogate for human respiratory pathology than does the rodent. This supplementary study provides useful data. No NOEL was evaluated for this "possible adverse effect". Aldous, 3/4/96.

1032-042 139033 [appendage to main report of that record] Monticello, T.M, K.T. Morgan, and J.A. Popp, "Formaldehyde-induced lesions in the respiratory tract: Comparison of F-344 rats with rhesus monkeys", Toxicologist 9:36 (1989). [S.O.T. annual meeting abstract]. Quoting from abstract: "The present studies were designed to provide data for a comparison of formaldehyde-induced responses in rats with previous findings in rhesus monkeys [i.e., Record No. 139033, above]. Twenty-four male F-344 rats were divided into 4 groups of 6 animals/group. Groups 1 and 2 (controls), were sham exposed to 0 ppm formaldehyde (HCHO) for 6 hr/day for either 4 d, or 6 wks (5 d/wk). Groups 3 and 4 were exposed to 6 ppm HCHO for either 4 d, or 6 wks (5 d/wk), respectively. The respiratory tract was assessed using histopathology. HCHO-induced lesions in the rat were characterized by epithelial degeneration, hyperplasia and squamous metaplasia, and were present in the anterior portion of the nasal passages, primarily confined to the lining of the lateral and middle meati. The nature and severity of HCHO-induced lesions in rats resembled those in monkeys similarly exposed to HCHO. However, in monkeys, nasal lesions were more widely distributed, extending to the nasopharynx. In addition, HCHO-induced lesions in the monkey continued distally to involve the trachea, carina and proximal portion of the major bronchi. These findings demonstrate clear differences in the distribution of formaldehyde-induced lesions between rats and primates, which should be considered when attempting to assess human risks from data generated in rodent inhalation toxicology studies." Aldous, 3/4/96.

1032-042 139034 Rusch, G.M., J.J. Clary, W.E. Rinehart, and H.F. Bolte, "A 26-week inhalation toxicity study with formaldehyde in the monkey, rat, and hamster", Bio/dynamics Inc., East Millstone, NJ. Published in Toxicol. Appl. Pharmacol. 68:329-343 (1983). Three species were housed 22 hr/day, 7 days/wk, for 26 wk in inhalation chambers at mean dose levels of 0, 0.19, 0.98, or 2.95 ppm formaldehyde (test atmosphere was generated by bubbling air through an "unstabilized, aqueous, 5%

solution" of formaldehyde, reportedly analyzed throughout the study, and showing no degradation). There were 20/sex of F-344 rats, 5 male Cynomolgus monkeys, and 10/sex of Syrian golden hamster per group [there were two complete control groups of all species, with staggered start times]. Parameters evaluated included body weights, clinical signs, and histopathology of lungs, nasal turbinates, and trachea. Reported clinical signs included hoarseness and congestion in 2.95 ppm monkeys. There were statistically significant decrements of bodyweights in male and female rats. The majority of 2.95 ppm rats showed squamous metaplasia/hyperplasia of nasal turbinates as well as basal cell hyperplasia, but there was no effect at 0.98 ppm. Squamous metaplasia/hyperplasia in monkeys had incidences of 0/12 in controls, 0/6 at 0.19 ppm, 1/6 at 0.98 ppm, and 6/6 at 2.95 ppm. Only the 2.95 ppm findings were considered by investigators to indicate a treatment effect in monkeys. This study is **inadequate** to fill a data gap. Investigators considered 0.98 ppm to be an overall NOEL, however this assessment is of limited value, since only a few parameters were evaluated, and histopathology findings in 0.98 ppm monkeys could be interpreted as a treatment effect. The nasal epithelium changes represent "possible adverse effects", but limitations of the study make further analysis unproductive. Aldous, 3/26/96.

ONCOGENICITY, RAT

1032-042 139030 Albert, R.E. et al., "Gaseous formaldehyde and hydrogen chloride induction of nasal cancer in the rat", published in JNCI 68:597-603 (1982). In the first lifetime study, male S-D rats were dosed with test atmosphere created by mixing formaldehyde vapor and HCl gas at high concentrations prior to diluting with air destined for the chambers. This was done to maximize the production of a reactive species, bis(chloromethyl)ether, (BCME). Reported chamber levels were 14.7 ppm formaldehyde and 10.6 ppm HCl, provided 6 hr/day, 5 days/week. A high yield of nasal tumors was obtained (about 80% by 2 yr). A subsequent study using male S-D rats was similarly conducted, however treatments included (1) premixed formaldehyde and HCl (similar concentrations as before, to maximize BCME production), (2) similar concentrations of formaldehyde and HCl, but not premixed, therefore minimizing BCME production, (3) 14.2 ppm formaldehyde alone, (4) 10.2 ppm HCl alone, or (5) air-sham controls. At the time of this submission, the study had been in progress for 588 days; long enough to show a response pattern for nasal tumor development. There was similar nasal tumor incidence in all groups containing formaldehyde. This suggests that the presence of HCl or BCME under these study conditions had little or no influence on nasal tumor yield elicited by about 14-15 ppm formaldehyde. This study was not designed to address FIFRA guidelines, but provides useful supplementary data. Aldous, 2/29/96.

1032-042 139031 Sellakumar, A.R. et al., "Carcinogenicity of formaldehyde and hydrogen chloride in rats", Toxicol. Appl. Pharmacol. 81, 401-406 (1985). This is a final report of the study under Record No. 139030, above. By term of study, it appeared that formaldehyde was principally or entirely responsible for the nasal tumors in rats, regardless of HCl or BCME contribution to test atmospheres. Most of the tumors were squamous cell type. Aldous, 2/29/96 (no worksheet).

50673-006 003733 A 1-paragraph reference to the rat and mouse inhalation study (1032-041 138989). No reviewable information. Aldous, 3/27/96.

ONCOGENICITY, MOUSE

****1032-041 138989** Pavkov, K.L., et al., "A chronic inhalation toxicology study in rats and mice exposed to formaldehyde", Battelle Columbus Laboratories (conducted for CIIT). Original report date: 9/18/81. Date of present submission: 12/31/81. **THIS IS THE REVIEW OF THE MOUSE DATA.** Paraformaldehyde was used to supply formaldehyde to B6C3F1 mice in inhalation chambers. Mice were exposed for 6 hours/day (5 days/week) for 24 months. Exposure levels were 0, 2, 6, or 15 ppm, with 120/sex/group. The following numbers/sex/group were killed at scheduled intervals: 10 at 6 months, 10 at 12 months, 20 (females only) at 18 months (high mortality in males precluded using them in this interim sacrifice), all remaining males and all but 20 females/group at 24 months, and all surviving females at 3 months post-exposure (month 27). No NOEL exists in the range tested. The major lesions were observed in nasal turbinates. Low dose effects were limited to rhinitis and adenitis of nasal epithelial tissues. Dysplasia and squamous metaplasia of nasal turbinate epithelial tissue, along with low levels of olfactory epithelial atrophy, were observed commonly at 15 ppm, and much less frequently at 6 ppm, beginning at 18 months. Two squamous cell carcinomas were observed in nasal turbinates of 15 ppm males at 24 months. In summary, lesions of nasal turbinates in mice were qualitatively similar to, but less severe than, those of rats in the parallel study. Study is **acceptable** to fill the oncogenicity data gap, but not for the rodent chronic study data gap. Nasal epithelial lesions, including carcinomas, are "**possible adverse effects**". No further information is required of this study. Kishiyama and Aldous, 2/13/96.

1032-042 138992 Horton, A.W., R. Tye, and K.L. Stemmer, "Experimental carcinogenesis of the lung. Inhalation of gaseous formaldehyde or an aerosol of coal tar by C3H mice", Kettering Laboratory, University of Cincinnati. J. Natl. Cancer Inst. 30:31-40 (1963). C3H mice, sex(s) unspecified, were exposed to formaldehyde vapors (generated from heated paraformaldehyde) at levels of 0, 0.05, 0.10, or 0.20 mg/l, three times weekly for 35 weeks. Each exposure was 1 hr. Some mice were examined for tracheobronchial epithelium histopathology after these exposures. Others were continued into a second phase, in which some control and formaldehyde-treated mice were exposed to coal tar aerosols in order to assess formaldehyde lung tumor induction. Only these respiratory tissues were evaluated. Some low-dose mice from phase I were administered 0.15 mg/l formaldehyde during phase II, to assess oncogenicity following additional exposure for up to 35 more weeks. No NOEL can be established, due to limitations of study design (especially the limited range of tissues evaluated). There were some treatment effects at the lowest dose tested after 35 weeks exposure [tracheobronchial epithelium basal cell hyperplasia and stratification of epithelial cells (a "possible adverse effect")]. The 0.20 mg/l dose caused high mortality. Formaldehyde treatment for 35 wk did not enhance tumor development due to subsequent coal tar inhalation. Due to multiple limitations in study design and reporting, the study does not address any data requirements. Kishiyama and Aldous, 2/28/96.

1032-029 133130 (exact duplicate of 1032-042:138992, above)

1032-045 139061 Spangler, F. and J.M. Ward, "Skin initiation/promotion study with formaldehyde in Sencar mice". Study location: Microbiological Associates (Bethesda, MD) in conjunction with NCI. Following the copy of this chapter is the cover page of the book from which this chapter was evidently taken: Formaldehyde: Toxicology, Epidemiology, and Mechanisms, Clary, J.J., J.E. Gibson, and R.S. Waritz, Eds., N.Y., Marcel Dekker, Inc., 1983. Sencar mice, 30 females/group, were treated in various combinations with or without an initiator (DMBA) or promoter [12-O-tetradecanoylphorbol-13-acetate (TPA)]. All test compounds were applied to back skin of mice with acetone, which was used as a negative control in some treatment combinations. Formaldehyde was tested for initiating and promoting capability. In all cases, formaldehyde was applied at 3.7-4% in acetone, however the

amount of this solution applied was not specified. All tests of initiators (including formaldehyde, when tested for such potential) were as a single dose. Promoters (including formaldehyde, when tested for such potential) were applied once or twice a week. This is an interim report, relating counts of skin papillomas as of the first 48 weeks of the study. Study found no evidence of formaldehyde as an initiating agent, nor as a complete carcinogen, however investigators considered there to be "a slight possibility that formaldehyde may be a very, very weak promoting agent", based on a very small tumor yield when formaldehyde was tested as a promoter in mice treated with DMBA (Fig. 3). Data are too reduced for further DPR analysis as of this interim report. Aldous, 3/6/96.

1032-045 139062 Krivanek, N.D., N.C. Chromey and J.W. McAlack, "Skin initiation-promotion study with formaldehyde in CD-1 mice", E.I. du Pont de Nemours & Company, Inc. Preceding the copy of this chapter is the cover page of the book from which this chapter was evidently taken: Formaldehyde: Toxicology, Epidemiology, and Mechanisms, Clary, J.J., J.E. Gibson, and R.S. Waritz, Eds., N.Y., Marcel Dekker, Inc., 1983. Formaldehyde was prepared for these studies by dissolving paraformaldehyde in water, then adding acetone to achieve a 10% formaldehyde solution in a 50:50 acetone:water mixture. This mixture was found not to show "formaldehyde-acetone condensation products" after 6 days, and solutions remained clear throughout the study; however stability was not otherwise assessed. Female mice were first treated on shaved dorsal skin with up to 10 mg formaldehyde, to assess skin irritation levels. Repeated doses of 2-5 mg caused mild to moderate skin irritation, whereas 1 mg caused only mild irritation. Based on this, formaldehyde was applied once at 5 mg/mouse to assess initiation potential. Formaldehyde promotor potential was tested at 0.1, 0.5, and 1.0 mg/mouse, applied 3 times/wk for 26 wk. Positive controls [150 mg benzo(a)pyrene (BaP) as initiator, 2.5 mg 12-O-tetradecanoylphorbol-13-acetate (TPA) as promoter], or negative control (acetone) were used as indicated. As expected, BaP/TPA gave a high tumor yield (28/29 mice, 9 of which had malignant tumors. Benign test site tumors were keratoacanthomas or squamous papillomas. No other combinations gave yields significantly different from controls. Thus the test is negative under study conditions, with the caveat that one cannot be certain whether formaldehyde underwent significant degradation to formic acid or other products. A retrospective analysis of test solutions, prepared as in this study, would improve the value of this supplementary study. Aldous, 3/7/96.

ONCOGENICITY, OTHER SPECIES

1032-045 139063 Dalbey, W.E., "Formaldehyde and tumors in hamster respiratory tract", Oak Ridge National Laboratory. Published in Toxicology 24:9-14 (1982). Male Syrian golden hamsters were used in two different studies. In all cases, formaldehyde was administered by inhalation, using heated paraformaldehyde as source material. Test atmospheres were sampled, and found close to nominal. The first study involved 132 untreated controls and 88 hamsters exposed to 10 ppm formaldehyde for 5 hr/day, 5 days/wk over a lifetime. Respiratory tract tissues were examined microscopically. This study found no oncogenicity, and very modest pathology of respiratory epithelium (hyperplasia and metaplasia were each noted in nasal epithelium of 5% of treated animals). The second study involved weekly doses of 30 ppm formaldehyde in various combinations with subcutaneous injections of 0.5 mg diethylnitrosamine (DEN), which was given once a week for 10 weeks. The 5 groups included 50 controls; 50 exposed to weekly formaldehyde treatments for life; 100 exposed only to DEN; 50 exposed to formaldehyde 48 hr before each DEN treatment, then continuing on formaldehyde weekly exposures for life; and (presumably 50) exposed to the 10-wk DEN treatment, then 2 wk later placed on weekly formaldehyde exposures for life. Only tumor data were discussed in the report. Nasal epithelial tumors

were uncommon, and not attributable to formaldehyde. The only noteworthy finding was an increase in tracheal tumors per tumor bearing animal, in hamsters exposed to formaldehyde 48 hr before each DEN treatment, then continuing formaldehyde weekly exposures for life. Investigators considered it possible that there was an interactive effect of formaldehyde and DEN during the initiation period. This finding indicates a "possible adverse effect", however the meaning is unclear, considering that the primary histopathology in another rodent (rat) occurs at the nasal turbinate level. Additional analysis of the non-tumor pathology would have improved the utility of this supplementary study. Aldous, 4/08/96.

NOTE: A study by Mueller et al. evidently found repeated exposure to the palate of rabbits to elicit carcinoma in situ (see Document No. 1032-039, Record No. 138971, p. 315).

REPRODUCTION, RAT

NOTE: There are no standard rat reproduction studies available. The following human study provides some supplementary data. Aldous, 3/22/96.

1032-046 139064 Cassidy, S.L., K.M. Dix, and T. Jenkins, "Evaluation of a testicular sperm head counting technique using rats exposed to dimethoxyethyl phthalate (DMEP), glycerol a-monochlorohydrin (GMCH), epichlorohydrin (ECH), formaldehyde (FA), or methyl methanesulphonate (MMS)". Arch. Toxicol. 53:71-78 (1983). Male Wistar rats were dosed once orally with 100 or 200 mg/kg formaldehyde (40% w/v, with 11-14% methanol as stabilizer). Rats were killed 11 days after dosing. Testes were weighed, homogenized, and sonicated. Sperm heads were counted, and percentages of abnormal heads were assessed. There was no effect at 100 mg/kg formaldehyde. At 200 mg/kg formaldehyde, there was a statistically significant increase in total sperm heads per gram testis, as well as an increase in percentage of abnormal sperm heads. Data indicated that "the induction of increased levels of abnormal sperm may be a measurable index of the mutagenic potential of a chemical for mammalian germ cells". Useful information: but does not fill SB-950 data gaps. Aldous, 4/08/96.

REPRODUCTION - (OTHER THAN RAT)

NOTE: There are no standard reproduction studies in species other than rat. The following study provides some supplementary data. Aldous, 3/22/96.

1032-046 139066 Ward, J.B. et al., "Sperm count, morphology and fluorescent body frequency in autopsy service workers exposed to formaldehyde", Mutation Res. 130:417-424 (1984). Report has two parts. In the first part, sperm samples from a small population of hospital autopsy service workers (11 men with TWA formaldehyde exposures averaging 0.61 to 1.32 ppm) and 11 matched controls were compared for sperm counts and abnormalities. No changes were detected. In the second part, 5 to 10 mice/group were dosed ip with formalin (100 mg/kg/day for 5 consecutive days), methanol (1 g/kg/day for 5 days), or cyclophosphamide (100 mg/kg, single dose). Abnormal morphologies were counted, including "lacks hook", "banana-shaped", "amorphous", "2-tails", and total percent abnormal sperm. Formaldehyde and methanol were both associated with increased banana-shaped sperm morphologies, however there was no significant difference in total abnormal sperm in these groups, and no other apparent anomalies. Investigators considered the mouse data to be negative. There is

not sufficient information to evaluate whether an "adverse effect" is indicated. Study does not address any SB-950 data gaps. Aldous, 3/19/96.

TERATOLOGY, RAT

1032-047 139068 Robinson, K., L. Pinsonneault, G. Goldsmith and B.G. Procter, "A teratological study of inhaled formaldehyde in the rat", Bio-Research Laboratories LTD, 9/9/85. Project No. 81581. Crl:COBS CD (SD) BR rats were dosed by whole body inhalation daily for 6 hr/day with 0, 2, 5, or 10 ppm formaldehyde over gestation days 6-15. An additional control group was not exposed to the inhalation chambers. There were 20-24 litters/group. The apparent maternal NOEL = 5 ppm (reduced body weight gain and reduced food consumption). The apparent developmental NOEL = 2 ppm (reduced ossification in the pelvic girdle, especially of the ischial bone). There were no serious developmental effects, nor widespread ossification delays. The study is **not acceptable, but upgradeable**. The following is requested: a statement of the relationship between the product produced by "purified paraformaldehyde" used in the study vs. representative technical formaldehyde. Clinical findings indicated a sialodacryoadenitis virus infection. Daily clinical observations were performed, however there was no table of clinical observation results. Tables of clinical observations (both summary and individual data) are requested, to allow an independent evaluation of the possible impact of this disease on the outcome of the study. No adverse effects are indicated at this time. Kishiyama and Aldous, 4/08/96.

1032-047 139069. Martin, W.J. "A Teratological Study of Inhaled Formaldehyde in the Rat". Reproductive Toxicology, Vol. 4, pp 237-239, 1990. A 3 page publication of Record No. 139068. No worksheet (Kishiyama, 8/16/95).

1032-047 139067. Robinson, K., et al. (range-finding study to Record No. 139068, addressed in review of that study). Aldous, 2/15/96.

1032-047 139070 Saillenfait, A.M., P. Bonnet and J. De Ceaurriz, "The effects of maternally inhaled formaldehyde on embryonal and foetal development in rats", Institut National de Recherche et de Se'curite', France. Published in Fd Chem. Toxic. 27 (8) 545-548, 1989. Formaldehyde, 37% aqueous ai, stabilized in 10% methanol, was administered by inhalation at 0, 5, 10, 20 or 40 ppm for 6 hours/day from days 6 through 20 of gestation to 25 mated female Sprague-Dawley rats/group. Maternal NOEL = 20 ppm (decreased maternal weight gain). Developmental NOEL = 10 ppm (decreased fetal body weights). There was an increase in unossified sternebrae at 40 ppm. Study is **not acceptable, and does not appear to be upgradeable**. There are no individual data, limited reproductive or body weight data, and no clinical observation or food consumption data. Also, GLP and QA sign-offs are lacking in this journal format. **No adverse effects are indicated.** Kishiyama and Aldous, 2/26/96.

TERATOLOGY, MOUSE

1032-047 139071 Marks, T.A., W.C. Worthy, and R.E. Staples. "Influence of Formaldehyde and Sonacide* (Potentiated Acid Glutaraldehyde) on Embryo and Fetal Development in Mice", Toxicology 22:51-58 (1980). [This is an NIEHS study conducted at Research Triangle Park Institute]. Fisher certified ACS formaldehyde solution (containing 12-15% methanol a preservative) was administered

by gavage at concentrations of 0, 74, 148 and 185 mg/kg/day to 76 (control) or 29-35 (treated groups) mated female outbred albino mice per group during days 6 through 15 of gestation. Fetuses were evaluated only for malformations, so that only a limited range of developmental effects was monitored. Mortality was 65% for the high dose group: maternal NOEL = 148 mg/kg/day. There were no definitive reproductive effects. No evidence of teratogenic effects was reported: apparent developmental NOEL = 185 mg/kg/day. Study is **not acceptable, and not upgradeable** (inadequate parameters evaluated, data are too reduced). Kishiyama and Aldous, 2/26/96.

1032-047 139072. Seidenberg, J.M., D.G. Anderson, and R.A. Becker. Validation of an In Vivo Developmental Toxicity Screen in the Mouse. Teratogenesis, Carcinogenesis, and Mutagens, 6:361-374 (1986). This study was undertaken to validate a developmental toxicity screening procedure in ICR/SIM mice. A series of 55 compounds was tested at dose levels well into the lethal range. Perinatal survival was the test criterion. Formaldehyde at 540 mg/kg/day over days 8-12 of gestation killed 11/30 dams without apparent effect on perinatal survival. This study does not supply essential information, and no worksheet is required. (Kishiyama and Aldous, 2/15/96).

TERATOLOGY, RABBIT

No study on file

TERATOLOGY, DOG

1032-046 139065 Hurni, H. and H. Ohder, "Reproduction study with formaldehyde and hexamethylenetetramine in beagle dogs", Laboratory of Bio-medical Research, Tierfarm Sisseln, Switzerland. Published in Fd. Cosmet. Toxicol. 11: 459-462 (1973). Pregnant beagles (10-11/group) were dosed with 0, 125, or 375 ppm formaldehyde in rations, giving estimated mean daily dosages of 0, 3.1 or 9.4 mg/kg/day formaldehyde (as 40% commercial solution, presumably containing methanol as stabilizer). Other dogs received mean estimated daily doses of 15 or 31 mg/kg/day hexamethylenetetramine (HMT, which yields formaldehyde upon metabolism). Treatments were on gestation days 4-56. Dogs were permitted to rear pups, which were inspected for external defects at birth and at 8 weeks. Most pups were further examined over an extended period averaging 7-8 months. There was no effect on fecundity. The mean numbers of stillborn pups/litter were slightly elevated in the 31 mg/kg/day HMT group. That group also had a reduction in live births surviving to weaning. No pups of any treatment groups indicated abnormal behaviors or appearance. There appeared to be a slight retardation in growth rates of high dose formaldehyde and HMT pups during lactation. [Maturing pups were later used for other investigations prior to eventual necropsies (no defects attributable to prenatal exposures were indicated)]. Because of the dosing regimen, this study most closely resembles a teratology study. No adverse effects are indicated. The design is so limited in scope that it does not address SB-950 data requirements. Aldous, 4/08/96.

GENE MUTATION

Microbial systems

****50673 008 39549** "Salmonella/Mammalian-Microsome Preincubation Mutagenicity Assay (Ames Test); Glyco Incorporated; Test Article 447:34-1." (Microbiological Associates, 9/27/82, Study No. T1802.502) Formaldehyde, clear liquid, 37% formalin, hydrolysis product of

1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin; tested in strains TA1535, TA1537, TA1538, TA98 and TA100 at 0, 3.0, 15, 75, 150 and 300 ug/plate with 20 minute preincubation in 600 ul; with and without rat liver activation; preliminary toxicity test in TA100 to 10,000 ug/plate, toxic at 305 or greater; triplicate plates, two trials with TA98 and TA100 with an increase in reversion rates, especially without activation, in both strains, both trials; initially reviewed as unacceptable because test material was not described. Submission of a partial duplicate of this report contains the notation that 37% formalin was tested - see 50673-013, Record # 54597. Acceptable. J. Remsen (Gee), 3/12/86 and 3/28/87.

EPA one-liner: Acceptable, positive responses in TA98 and TA 100 with and without metabolic activation.

50673-005 039519 Exact duplicate of Record No. 039549, above.

1032-048 139075 Schmid, E., W. Göggelmann, and M. Bauchinger, "Formaldehyde-induced Cytotoxic, Genotoxic and Mutagenic Response in Human Lymphocytes and Salmonella typhimurium". Mutagenesis 1(6):427-431 (1986). Formaldehyde (37% plus 10% methanol) was tested with Salmonella strain TA100 ± S9 activation by plate incorporation (0 to 1.5 mM) and by preincubation (0 to 0.3 mM). Human male lymphocytes stimulated with PHA were exposed for 1 hr after being in culture for 44 hr with a total time of 69 hr at 0 to 1.0 mM. An increase in the incidence of chromosomal aberrations and chromatid exchanges in human lymphocytes and of revertants for S. typhimurium strain TA100 is reported. "Possible adverse effect". Unacceptable (no individual data). Gee, 3/26/96.

1032-006 003728 "Hazardous and Toxic Effects of Industrial Chemicals - Formaldehyde: Harmful Effects - Gene Mutation in Neurospora cassida." (Petrolite Corp. 1979) References to publications, no original data. **Unacceptable.** J. Remsen (Gee), 3/22/85.

Mammalian systems

**** 50673 008 39555** "Mouse Lymphoma L5178Y Cell TK Locus Assay for Mutagenicity; A Study with Formaldehyde." (DuPont, 7/28/80, Haskell Laboratory Report No. 581-80). Formaldehyde, 37%, ACS Grade, Fisher Scientific; tested at 0, 0.1, 0.5, 1, 5, 10 or 20 ug/ml without activation only, four trials; an increase in mutation frequency was reported, especially at 10 and 20 ug/ml; initially reviewed as unacceptable because no protocol was included, only a citation from the literature. After further consideration, considering the known effects of formaldehyde, the study has been upgraded to acceptable (protocol still not included). J. Remsen (Gee), 3/13/86 and 5/28/87.

50673-005 039524 Duplicate of 039555, above.

50673-003 039554 Supposedly this volume has a table of mutagenicity data. I do not find it, nor would the data likely have bearing on data gap or hazard assessment status. Aldous, 3/26/96.

CHROMOSOMAL EFFECTS

**** 50673 008 39558** "Cytogenicity Study - Chinese Hamster Ovary (CHO) Cells in vitro; Test Article 447:34-1." (Microbiological Associates, 9/28/82, Study No. T1802.338) Formaldehyde, 447:34-1, 37% formalin; tested without activation at 0, 28.43, 37.91 or 50.55 nl/ml and with activation at 0, 75.82, 101.09 or 134.79 nl/ml, 4-hour incubation, 18-hour harvest; 50 cells scored per concentration for

aberrations; acceptable; concentration-dependent increase in chromosomal aberrations per cell is reported. Initially reviewed as unacceptable because test material was not described. This deficiency was satisfied with the submission of Document 50673-013, Record # 54604 (a partial duplicate of # 39558 containing the notation that 37% formalin was used in the study.) J. Remsen (Gee), 3/13/86 and 3/28/87.

EPA one-liner: Acceptable, Positive with or without metabolic activation in Chinese hamster ovary cells.

50673-005 039527 Duplicate of 039558, above.

1032-048 139075 (The 1-liner for this study, which included both gene mutation and chromosomal effects is found above under "Gene Mutation".

1032-048 139077 Dallas, C.E., M.J. Scott, J.B. Ward Jr., J.C. Theiss. "Cytogenic Analysis of Pulmonary Lavage and Bone Marrow Cells of Rats after Repeated Formaldehyde Inhalation". Journal of Applied Toxicology 12(3): 199-203 (1992). Male Sprague-Dawley rats were exposed to 0, 0.5, 3, or 15 ppm formaldehyde (from depolymerization of paraformaldehyde) by inhalation 6h/day, 5 days/wk for 1 and 8 wk, 4-5 rats/dose. Scored 50 cells/rat. Increased incidence of chromosomal aberrations in the pulmonary lavage cells at 15 ppm, but not in the bone marrow of rats that inhaled formaldehyde, was reported. Unacceptable (some data were presented as graphs), "possible adverse effect". Gee, 3/26/96.

1032-048 139078 Natarajan, A.T., F. Darroudi, C.J.M. Bussman, A.C. van Kesteren-van Leeuven, "Evaluation of the mutagenicity of formaldehyde in mammalian cytogenetic assays in vivo and in vitro". Mutation Res. 122:355-360 (1983). Formaldehyde (from paraformaldehyde) was positive in chromosomal aberrations (gaps, breaks and fragments, and exchanges) and in SCE's in CHO cells over the concentration range of 0.003 to 0.024 ml/ml. Effects were consistently greater without S9 than with S9 in medium. The in vivo tests in male and female CBA mice injected ip at 0, 6.25, 12.5 or 25 mg/kg [micronuclei in polychromatic erythrocytes in mouse bone marrow cells, and chromosomal aberrations in mouse bone marrow cells - both after exposure times of 16 and 40 hr] were negative. Results indicate a "possible adverse effect", however are consistent with other studies, which demonstrate a high intrinsic reactivity of formaldehyde, such that comparatively little unreacted formaldehyde reaches the nucleus. Study is possibly upgradeable, with submission of individual data. Gee, 3/27/96.

DNA DAMAGE

50673-013 57201 "Induction of DNA Synthesis." (Lab not stated, 1983, CTFA Study YE 692) Glydant 40-700 (TSIN G0047.03) and formaldehyde (G0226.01); rat primary hepatocytes for unscheduled DNA synthesis; formaldehyde at 0, 27.3 or 40 ug/ml by infusion or 20 ug/ml initial concentration and Glydant at 0.144 ul/ml; 20-hour exposure; duplicate cultures, scored 50 cells per concentration; infusion resulted in fewer attached cells; report states no increase in unscheduled DNA synthesis but all data are missing for the incomplete report. Unacceptable, complete report requested. J. R. Gee, 5/29/87.

**50673-008 39561 "Unscheduled DNA Synthesis in Rat Hepatocytes; Test Article 447:34-1." (Microbiological Associates, 12/3/82, Study T1802.380002) Formaldehyde, 37% formalin; tested at

0.0005, 0.001, 0.005, 0.01 or 0.04 ul/ml, 18 hours; no increase in UDS reported; acceptable. Initially reviewed as unacceptable based on the lack of description of the test material. This information was provided in the letter of February 3, 1987. Document 50673-012. J. Remsen (Gee),3/14/86 and 3/28/87.

EPA one-liner: Acceptable, Negative. No increase in UDS in rat hepatocytes.

50673-005 039530 Duplicate of 039561, above.

1032-006 35785 "Hazardous and Toxic Effects of Industrial Chemicals - Formaldehyde: Harmful Effects - DNA Damage and Repair in E. coli B/R." (Petrolite Corp., 1979) Reference to published information [Rosenkranz, H.S., "Formaldehyde as a possible carcinogen", Bull. Env. Contam. Toxicol. 8:242, (1972)]. Report indicated that E. coli B/R had increased mutations with formaldehyde treatment. J. Remsen (Gee), 3/22/85.

GENOTOXICITY SUMMARY: Studies indicate that formaldehyde is mutagenic in microbial and mammalian cell systems in vitro, and that it causes chromosomal damage in mammalian cells in vitro. Unscheduled DNA synthesis studies with formalin are negative. No further studies are required at this time but the complete report for Record 50673:57201 is requested to complete the data base on file at DPR

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NEUROTOXICITY

Not required at this time.

--- End of FIFRA-mandated study type reviews ---

GENOTOXICITY-RELATED INFORMATION: NOT FIFRA-TYPE DATA

1032-029 133133 Auerbach, C., M. Moutschen-Dahmen, and J. Moutschen, "Genetic and cytogenetical effects of formaldehyde and related compounds". Mutation Res. 39:317-362 (1977). A general discussion of effects of formaldehyde on Drosophila, bacteria, and several other species. No reviewable data are included. Aldous, 3/18/96.

1032-048 139076 (Exact duplicate of 029:133133, above)

MISCELLANEOUS SUBCHRONIC STUDIES, NOT REQUIRED UNDER SB-950

1032-029 133139 Coon, R.A. et al., "Animal inhalation studies on ammonia, ethylene glycol, formaldehyde, dimethylamine, and ethanol", Toxicol. Appl. Pharmacol. 16:646-655 (1970). Small numbers of rats, guinea pigs, rabbits, monkeys, and dogs were exposed for 90 days continuously to 4.6 mg/m^3 formaldehyde. Report states that "lungs of all species consistently showed varying degrees of interstitial inflammation, and the hearts and kidneys from guinea pigs and rats showed focal chronic inflammatory changes. It was uncertain whether these change were caused by the formaldehyde inhalation." No worksheet is appropriate (no data provided). Aldous, 3/18/96.

HUMAN EPIDEMIOLOGICAL STUDIES (CHRONIC/CANCER)

1032-042 139035 Acheson, E.D. et al., "Formaldehyde in the British Chemical Industry: An occupational cohort study", The Lancet 3/17/84, pp. 611-616. Study does not identify cancer risks due to formaldehyde. Not a SB-950 study: no worksheet. Aldous, 3/4/96.

1032-042 139036 Blair, A. et al., "Mortality among industrial workers exposed to formaldehyde", JNCI 76:1071-1084 (1986). This NCI historical cohort study analyzed about 600,000 person-years of exposure to formaldehyde. Many of the analyses divided workers into exposure groups, based on work assignments and environmental controls in place over the course of the study. No remarkable associations between exposure and increased cancer risks could be ascertained. Two weaknesses of this study noted by investigators were (1) cohort studies are inherently limited at detecting treatment-related increases in uncommon tumors, and (2) this study did not evaluate the large confounding effects of tobacco use. Not an SB-950 study: no worksheet. Aldous, 3/5/96.

1032-042 139037 Blair, A. et al., "Letters to the Editor: Cancers of the nasopharynx and oropharynx and formaldehyde exposure" in JNCI 78:191. This letter notes that although the above study Record No. 139036 (above) did not indicate formaldehyde-caused cancers when aggregate data were evaluated, it should be noted that an unusual number of cancers of the nasopharynx and oropharynx occurred in a single plant at which formaldehyde exposure was associated with high levels of dusts. Writers recommended the value of undertaking a case-control study to evaluate the effects of high dust exposure in the presence of formaldehyde. On the following page, a rebuttal to this letter was published, prepared by a representative of the plant at which 4 individuals worked who suffered nasopharynx cancers following exposures to particulates plus formaldehyde. Major concerns were: (1) there are no other epidemiological studies indicating a relationship between nasopharangeal cancer and formaldehyde/particulate exposure, (2) there were similar exposure scenarios at other plants, but no nasopharynx tumors, (3) the highest exposures at the cited plant had occurred prior to 1946, at which time new engineering controls were established, which markedly reduced exposures. All of the 4 affected workers were hired in or after 1949. Of the 931 persons employed prior to 1946, none developed nasopharangeal cancer. The rebuttal also suggested that "particulates" is so loosely defined a term that it would not be easy to construct a meaningful case-control study as proposed. Not an SB-950 study: no worksheet. Aldous, 3/5/96.

1032-042 139038 Coggon, D., B. Pannett, and E.D. Acheson, "Use of job-exposure matrix in an occupational analysis of lung and bladder cancers on the basis of death certificates". JNCI 72:61-65 (1984). Formaldehyde was one of several industrial exposure chemicals evaluated in a case-control study, which considered all males under the age of 40 who died in England or Wales during the period 1975-1979. "Cases" were men for whom "cause of death" was recorded as cancer of the trachea, bronchus, or lung [each of the three cancer sites were considered separately]. For each "case", an attempt was made to identify 2 "controls", matched as closely as possible to that case's birth and death dates, but having primary cause of death from any other cause. In the preliminary analyses, occupations were judged by a trained industrial hygienist as to whether or not they involved exposure to formaldehyde (irrespective of amount). In the analyses for bronchial cancer, there emerged a relative risk of 1.5 for occupations involving formaldehyde exposure (statistically significant, $p < 0.001$). Secondary analyses used men with "high exposure" to the same series of pollutants as "cases". That analysis yielded a relative risk of 0.9 for "high" formaldehyde exposure. Investigators' conclusion was that "the absence of a risk in jobs with high exposure is against a direct causal mechanism". It is noteworthy that the study was sensitive enough to identify asbestos [any exposure level] or asbestos

[high exposure] to be associated with bronchial cancer, even though data did not adjust for smoking habits. Not an SB-950 study: no worksheet. Aldous, 3/6/96.

1032-042 139039 Decoufle, P., "Cancer risks associated with employment in the leather and leather products industry", Arch Environ. Health 34:33-37 (1979). Study found increases in urinary bladder cancer, buccal cancer, laryngeal cancer and malignant lymphoma among leather workers. Primary candidate for causality was azo and other synthetic dyes, although formaldehyde was noted as one of several possible tanning materials. Not an SB-950 study: no worksheet. Aldous, 3/6/96.

1032-042 139040 Doll, R. and R. Peto, "Mortality among doctors in different occupations", British Medical Journal 1:1433-1436 (1977). It is not clear why this article is included in the volume. There is no useful information here relating to medical specialists' exposure to formaldehyde *per se*. Not an SB-950 study: no worksheet. Aldous, 3/6/96.

1032-042 139041 Doll, R. and R. Peto, "Mortality in relation to smoking: 20 years' observations on male British doctors", British Medical Journal 2:1525-1536 (1976). It is not clear why this article is included in the volume. There is no useful information here relating to medical specialists' exposure to formaldehyde per se. This study does, however, provide potentially useful information about the influence of smoking on cancers at several sites (respiratory tract and otherwise), as well as on non-cancer endpoints such as ischemic heart disease. Probably the primary usefulness of this study is to demonstrate that a cohort study on this scale (smoking habits and causes of death were examined, with an initial pool of 34,440 men) offered sufficient power to clearly identify several health outcomes of a risk factor. Another primary usefulness of this study is to demonstrate that smoking habits have a profound influence on respiratory tract pathology, and thus should be factored into study designs to evaluate formaldehyde-related outcomes. Not an SB-950 study: no worksheet. Aldous, 3/6/96.

1032-043 139042 Fayerweather, W. E., S. Pell and J. R. Bender, "Case control study of cancer deaths in du Pont workers with potential exposure to formaldehyde", in FORMALDEHYDE: Toxicology, Epidemiology, Mechanisms (Clary, J. J., J. E. Gibson, and R. S. Waritz, Eds.), Marcel Dekker, Inc., New York (no date, latest bibliographical citation was 1982). Cancer deaths from 1957 to 1979 at 8 sites were evaluated. There were 481 cancer deaths, 142 in workers with potential formaldehyde exposure. Odds ratios considered smoking habits in respective case and control groups (typically smoking habit differences were so small that unadjusted data were presented). Generally the degree of formaldehyde exposure was split only into "intermittent" or "continuous" designation. The vast majority of cases smoked to some extent (Table 4), increasing odds ratios for lung, bronchial, or tracheal cancers to about 2 to 8, depending on amount smoked. Investigators determined that the study was powerful enough to detect a 1.5-fold overall cancer increase or a 2.3-fold increase in lung cancer in workers with at least 5 yr exposure (80% confidence in both cases). The test had very limited sensitivity for less common cancers (pp. 97, 104). No evidence of increased overall cancer risk or of plausibly treatment-related specific cancers was identified. Study appears to be of limited value. Not an SB-950 study: no worksheet. Aldous, 3/21/96.

1032-043 139043 [A study on phenoxyacids and chlorophenols with respect to human nasal and nasopharyngeal cancers]. No direct relationship to formaldehyde evaluation. Not an SB-950 study: no worksheet. Aldous, 3/21/96.

1032-043 139044 [Harrington, J. M. and Shannon, H.S., "Mortality study of pathologists and medical

laboratory technicians", British Medical Journal, 8 Nov. 1975. An increase in lymphatic plus hematopoietic neoplasms in male English pathologists was noted. There was no discussion of formaldehyde as a likely contributing factor. This study has no apparent usefulness toward hazard identification. Not an SB-950 study: no worksheet. Aldous, 3/21/96.

1032-043 139045 Hayes, R. B. et al., "Cancer of the nasal cavity and paranasal sinuses, and formaldehyde exposure", Int. J. Cancer 37:487-492 (1986). "Cases" were 116 males newly diagnosed with nasal cancers at any of the 6 major institutions in the Netherlands for treatment of head and neck tumors: these were compared to age-stratified "controls". There was an increase in cases associated with presumed formaldehyde exposure (based on job titles), which could not be explained on the basis of other plausible causes (such as smoking or wood dust exposure). The prevalent tumor type associated with the increases was squamous cell carcinoma. Investigators recognized the limitations of the study design (small sample sizes, exposure levels only roughly characterized, few controls for other risks), but considered that data warrant further study. Not an SB-950 study: no worksheet. Aldous, 3/21/96.

1032-043 139046 Jensen, O.M. and Andersen, S. K. "Lung cancer risk from formaldehyde" (a letter to the editor of The Lancet, April 17, 1982). A small study of Danish physician lung cancer incidence found no increased odds ratios in any specializations noted. Limitations of small sample size were noted. Not an SB-950 study: no worksheet. Aldous, 3/21/96.

1032-043 139047 Levine, R. J. et al., "Mortality of Ontario undertakers: A first report", in Formaldehyde: Toxicology, Epidemiology, and Mechanisms, Clary, J. J., J. E. Gibson, and R.S. Waritz, Eds., N.Y., Marcel Dekker, Inc., 1983, pp. 127-146. This study evaluated death records of 337 undertakers. There were no evident changes in tumor incidences in various organs or body locations. Not an SB-950 study: no worksheet. Aldous, 3/21/96.

1032-043 139048 Levine, R. J. et al., Journal of Occupational Medicine 26:740-746 (1984). This is the publication at the completion of the study first reported in Record No. 139047, above. There were no cancer excesses among undertakers. Not an SB-950 study: no worksheet. Aldous, 3/21/96.

1032-043 139049 Liebling, T. et al., "Cancer mortality among workers exposed to formaldehyde", American Journal of Industrial Medicine: 5:423-428 (1984). Twenty-four employees from a Monsanto plant in Massachusetts who died between 1/1/76 and 12/31/80 were the test population, from which various cancer outcomes were compared against the US proportionate mortality ratios (PMR's). Only 10 of these men died of malignancies of any kind. Smoking was not considered in the evaluation. Many of the workers worked in many areas of the plant, and were exposed to a great variety of chemicals other than formaldehyde. There were statistically significant increases in incidences of colon/rectal cancer and of buccal/pharyngeal cancer (4 and 2 cases, respectively). Investigators considered these results to provide "evidence of formaldehyde's carcinogenicity". It would appear that a study of this small magnitude is of limited value in hazard assessment. Not an SB-950 study: no worksheet. Aldous, 3/21/96.

1032-043 139050 Marsh, G.M., "Proportional mortality patterns among chemical plant workers exposed to formaldehyde", British Journal of Industrial Medicine 39:313-322 (1982). Workers at 5 areas of a large Monsanto operation in Springfield, MA who died between 1950 and 1976 formed the study group. Of these, 136 had been employed for at least one month in an area having significant formaldehyde exposure. Twenty-two of these men died of malignant neoplasms. No unusual

distribution pattern was evident. Due to small sample size, lack of exposure measurements, and lack of control for smoking, this study appears to have little interpretive value. Not an SB-950 study: no worksheet. Aldous, 3/21/96.

1032-043 139051 Moss, E. and W.R. Lee, "Occurrence of oral and pharyngeal cancers in textile workers", British Journal of Industrial Medicine 31:224-232, 1974. There was a reported excess of oral and pharyngeal cancers among textile workers, most notably among fiber preparers (more in the wool industry than in cotton). Formaldehyde was not the most suspect factor in these excesses: high dust levels was proposed as a major factor. (See Document No. 1032-038, pp. 35-36, for discussion on formaldehyde in textile operations). Future re-examinations were expected, which would take tobacco use into account. This report appears to have little value in formaldehyde hazard evaluation. Not an SB-950 study: no worksheet. Aldous, 3/21/96.

1032-043 139052 Olsen, J. H. et al., "Occupational formaldehyde exposure and increased nasal cancer risk in man", Int. J. Cancer 34:639-644 (1984). A large scale case-control study was undertaken from the Danish Cancer Registry. "Cases" were 839 cases of cancers of the nasal cavities, sinuses, and rhinopharynx diagnosed during 1970-1982. "Controls" were 2465 cases of cancers (excluding upper respiratory system) of the same period. Formaldehyde exposure was determined as "certain" for some industries or occupations, or "probable" for several others. There was no adjustment for tobacco use patterns, nor was there any attempt to evaluate probable exposure levels. Many of the "certainly" exposed persons were involved lumber or carpentry fields, and involved exposures to both formaldehyde and wood dusts. Both of the latter were associated with increased relative risks of the above upper respiratory epithelial tumors. Occupations which involved exposures to both formaldehyde and wood dusts had particularly high risk ratios, whereas formaldehyde risk ratios among persons not occupationally exposed to wood dusts was only slightly (not statistically significantly) elevated over controls. Investigators considered this study to be comparatively robust, and indicative of an appreciable risk due to formaldehyde. Not an SB-950 study: no worksheet. Aldous, 3/21/96.

1032-044 139054 Stayner, L.T. et al., "A retrospective cohort mortality study of workers exposed to formaldehyde in the garment industry", Amer. J. Ind. Med. 13:667-681 (1988). Formaldehyde levels of about 0.15 ppm prevailed in the workplaces as of the time of the study: past exposures may have been much higher. Most of the study population (609 deaths, 186 of them due to malignancies) consisted of white females. SMR's were based on U.S. mortality data. This study showed an increase in buccal cavity malignancies (4 observed vs. 1.2 expected) and connective tissue malignancies (4 observed vs. 1.1 expected). Other respiratory-related tumors were near to expected incidences. The buccal tumors in particular were considered to be inconclusive, but cause for concern. Not an SB-950 study: no worksheet. Aldous, 3/22/96.

1032-044 139055 Stayner, L.T. et al., "Proportionate mortality study of workers in the garment industry exposed to formaldehyde", Amer. J. Ind. Med. 7:229-240 (1985). This is the initial phase of the study more fully reported in Record No. 139054, above. No worksheet. Aldous, 3/22/96

1032-044 139056 Vaughan, T.L. et al., "Formaldehyde and cancers of the pharynx, sinus and nasal cavity: I. Occupational exposures", Int. J. Cancer 38:677-683 (1986). Cases were individuals from 13 western Washington state counties who were diagnosed with cancers of the oro-and hypopharynx, nasopharynx, or sinus and nasal cavity. Controls were from the same area. The study considered smoking and drinking as confounding factors, and classified formaldehyde exposure as "background",

low, medium, or high based on occupational status. There were no statistically significant increases in tumors studies, although some of the odds ratios were over 1.0. Not an SB-950 study: no worksheet. Aldous, 4/08/96.

1032-044 139057 Vaughan, T.L. et al., "Formaldehyde and cancers of the pharynx, sinus and nasal cavity: II. Residential exposures", Int. J. Cancer 38:685-688 (1986). The same population was used as in Record No. 139056, above, however the focus of this study was possible effects of formaldehyde exposure from construction products in their homes. The primary association of interest was whether or not the subject lived in a mobile home. The odds ratio for nasopharangeal tumors was elevated, particularly for persons living 10 or more years in a mobile home (odds ratio = 5.5, with 95% CI = 1.6-19.4). The relationship was considered rather strong, yet to be interpreted with caution, since only a few cases were evaluated. Not an SB-950 study: no worksheet. Aldous, 3/22/96.

1032-044 139059 Walrath, J. and Fraumeni, J. F., "Proportionate mortality among New York embalmers", in Formaldehyde Toxicity, Gibson, J. E., Editor, Washington D.C., Hemisphere Publishing Co., 1983 (pp. 227-236). Death certificates were examined from 1106 New York embalmers. Most were white males, the primary group examined. Of the 210 white males dying of malignant neoplasms, 8 died of skin tumors (compared to 3.2 expected). Of these, 4 were malignant melanoma, and 3 were squamous cell carcinomas. There were no increases in tumors of the respiratory tract. Investigators noted that other chemicals were used in the embalming process, which could contribute to risk. They determined that further studies were indicated. Not an SB-950 study: no worksheet. Aldous, 3/22/96.

1032-044 139058 Walrath, J. and Fraumeni, J. F., "Proportionate mortality among New York embalmers", Int. J. Cancer 31:407-411 (1983). This appears to be a slightly later version of Record No. 139059, above. Slightly more death certificates were available at the time of the present report, however the conclusions were the same in both records. Aldous, 3/22/96.

1032-039 138973 Wendlick, J., "Formaldehyde: Summary of epidemiology studies", in Proceedings of the Seventeenth Washington State University International Symposium of Particleboard, March 29-31, 1983. This presentation highlights some of the major epidemiological studies available as of that date. Not an SB-950 study: no worksheet. Aldous, 3/22/96.

GENERAL RISK ASSESSMENT OR GENERAL REVIEW ARTICLES

1032-029 133132 Griesemer, R.A. et al., "Report of the Federal Panel on Formaldehyde", Environ. Health Perspect. 43:139-168 (1982). This article was not reviewed, since it was comparatively old, and since it is not a "study". Abstract notes that nasal cancers in F-344 rats at dose levels near to those of exposed human workers suggest that there might be a carcinogenic risk to humans. (No DPR review); Aldous, 3/18/96.

1032-048 139073 Boreiko, C.J., D.B. Couch, and J. A. Swenberg, "Mutagenic and carcinogenic effects of formaldehyde", in Genotoxic Effects of Airborne Agents (Tice, Costa, and Schaich, Eds., Plenum Press, New York). Book was dated prior to June 8, 1982. Little or no unique information. Autoradiographs of rat nasal area distribution of ^{14}C labeling following an exposure session with 15 ppm 14C-formaldehyde shows the pattern of label deposition. Aldous, no worksheet. 3/20/96.

1032-048 139074 Ma, Te-Hsiu and M.M. Harris "Review of the genotoxicity of formaldehyde", Mutation

Res. 196:37-59 (1988). No new data, no worksheet. Aldous, 3/20/96.

1032-038 138970 (NIOSH report of December 1976) "Criteria for a recommended standard. . . Occupational Exposure to Formaldehyde". Report may contain useful worker exposure or worker toxicity data, suitable for risk assessment. There are no reviewable data for SB-950 evaluation. Aldous, 3/20/96.

1032-037 138962 Gibson, J. E., "Mechanisms of formaldehyde toxicity and carcinogenicity in laboratory animals", in Proceedings of the Sixteenth Washington State University International Symposium of Particleboard, March 30-April 1, 1982. Contains overview of results of 1981 CIIT rat and mouse studies conducted at Battelle Memorial Institute, brief toxicology evaluation, and risk assessment. Not an SB-950 study: no worksheet. Aldous, 3/20/96.

1032-037 138963 "Report on the consensus workshop on formaldehyde", Environ. Health Perspect. 58:323-381 (1984). U.S. EPA and NCTR coordinated a workshop to evaluate health effects of formaldehyde. This substantial document discusses animal toxicity studies, worker exposure data, and offers risk assessment. Not an SB-950 study: no worksheet. Aldous, 3/20/96.

1032-037 138964 "Report of the Federal Panel on formaldehyde", Environ. Health Perspect. 43:139-168 (1982). Discussion of animal toxicity studies and limited human epidemiological studies available at that date. Not an SB-950 study: no worksheet. Aldous, 3/20/96.

1032-037 138965 "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Industrial Chemicals and Dyestuffs", Volume 29 (WHO IARC Working Group meetings in Lyon, Oct. 1981). Publication discusses chemical characteristics of formaldehyde, major technical products, industrial uses, various governmental exposure limits, potentially exposed occupations, occupational exposure concentrations reported, animal toxicity studies, and human epidemiological data. Not an SB-950 study: no worksheet. Aldous, 3/20/96.

1032-037 138966 IRIS printout of 6/19/95 for formaldehyde. Contains some summaries of major animal toxicity studies. Oncogenicity classification is "B1" ("probable human carcinogen"), based on "limited evidence in humans" and "sufficient evidence in animals" (p. 00151). "Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products." This report discusses key epidemiological studies. Because of the recent date, this may be a particularly useful reference for risk assessment. Not an SB-950 study: no worksheet. Aldous, 3/20/96.

1032-037 138967 Newell, G. W., "Overview of Formaldehyde", in Formaldehyde Toxicity, Gibson, J. E., Editor, Washington D.C., Hemisphere Publishing Co., 1983. This is a brief review of sources of formaldehyde, and occupational exposure and human health effects. Not an SB-950 study: no worksheet. Aldous, 3/20/96.

1032-044 139053 Siegel, D. M. et al., "Formaldehyde risk assessment for occupationally exposed workers", Regulatory Toxicology and Pharmacology 3:355-371 (1983). Clement Associates, Inc. risk assessment under contract with OSHA. Several animal and human studies were discussed, however primary study used for quantitative risk assessment is the 1981 CIIT chronic rat inhalation study (Document No. 1032-041). Not an SB-950 study: no worksheet. Aldous, 3/22/96.

1032-039 138971 Restani, P. and Galli, C.L., "Oral toxicity of formaldehyde and its derivatives", Crit. Rev. Toxicol. 21:315-328 (1991). Discussion of use patterns of formaldehyde, its metabolism and toxicity. Discussion of toxicity of hexamethylenetetramine and some formaldehyde derivatives. No reviewable studies are included: no worksheet. Aldous, 3/22/96.

1032-039 138972 Squire, R.A. and Cameron, L. L., "An analysis of potential carcinogenic risk from formaldehyde", Regulatory Toxicology and Pharmacology 4:107-129 (1984). Authors caution about depending on rat tumor data to assess human cancer risk, given substantial anatomical and physiological differences between species. They recommend that risk assessment consider all available data. Summaries of human and animal toxicity data are presented. Not an SB-950 study: no worksheet. Aldous, 3/22/96.

1032-039 138974 WHO "Environmental Health Criteria 89" document on Formaldehyde. This may be useful for risk assessors, as it contains information on sources of exposures, measured exposure levels, metabolism, toxicity in animals and man, and human health evaluation. Not an SB-950 study: no worksheet. Aldous, 3/22/96.

1032-034 138960 "Evaluation of the potential carcinogenicity of formaldehyde", the EPA Carcinogen Assessment Group final draft (June 1988). Not an SB-950 study: no worksheet. Aldous, 3/22/96.

1032-035 138961 Final Draft, "Formaldehyde Risk Assessment Update", June 11, 1991 (OTS, U.S. EPA). This may be one of the more complete and recent documents useful for risk assessment. Not an SB-950 study: no worksheet. Aldous, 3/22/96.

1032-031 138952 d'A. Heck, H. et al., "Formaldehyde toxicity - New understanding", Crit. Rev. Toxicol. 20:392-426 (1990). Much of the focus of this review is on the nature of formaldehyde reactivity, plus other features of interest to risk assessment. Not an SB-950 study: no worksheet. Aldous, 3/22/96.
NOTE: The first part of this volume contains a substantial index of toxicity data submitted for formaldehyde.

1032-032 138954 "Health and Environmental Effects Profile for Formaldehyde", Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, ORD, U.S. EPA, Cincinnati, OH. An Oct. 1985 profile of formaldehyde, of possible use for risk assessment. Not an SB-950 study: no worksheet. Aldous, 3/22/96.

1032-033 138955 "Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde", April 1987 document by OPTS, U.S. EPA. Not an SB-950 study: no worksheet. Aldous, 3/22/96.

1032-042 139029 Swenberg, J. A. et al., "Non-linear biological responses to formaldehyde and their implications for risk assessment". Carcinogenesis 4:945-952 (1983). Some pages are missing. No SB-950 worksheet. Aldous, 2/29/96.

1032-042 139032 Monticello, T.M. and K. T. Morgan, "Cell proliferation and formaldehyde-induced respiratory carcinogenesis", Risk Analysis 14 (3):313-319 (1994). This is a brief, but current commentary addressing the need to consider DNA-protein cross-linking and cell proliferation activities (both of which are non-linear with respect to exposure in the range of 0 up to 10 or 15 ppm atmospheric concentrations). This is not a study, hence no worksheet. (Potentially useful for risk assessment).

Aldous, 3/1/96.

FEDERAL REGISTER EVALUATIONS:

Volume entitled: "Formaldehyde Federal Register Items, Resubmit 7/30/96. No Document or Record Numbers are assigned to the volume. DPR does not routinely index these federal documents. This is a compilation of three major documents submitted by Technology Sciences Group, Inc. on behalf of associated data generators, accompanying a Nov. 26, 1996 cover letter from A. Lawyer to C. Cummins. The documents, particularly the lengthy 1987 "Final Rule, summarized major human and animal studies and acknowledged various points of view in their interpretations. DPR does not routinely index these federal documents.

1. Advanced Notice of Proposed Rulemaking, including a "Determination of Significant Risk (1984). This was an EPA document (40 CFR Part 765, pp. 21870-21898).
2. Final Rule (1987), produced by OSHA. This document (29 CFR Parts 1910 and 1926, entitled "Occupational exposure to formaldehyde: Final rule", dated Dec. 4, 1987, pp. 46168-46312) notes the transfer of primary responsibility over evaluation of occupational risks from U.S. EPA to OSHA on 2/18/86 because of OSHA's jurisdiction in the area (see p. 46170). This document considered that there was "sufficient" evidence that formaldehyde was an animal carcinogen, and that formaldehyde was a "probable" human carcinogen (p. 46170). This ruling reduced the 8-hr TWA exposure limit from 3 ppm to 1 ppm. A serious consideration was the observation that the 3 ppm group in the major rat inhalation study (CIIT study by Pavkov *et al.*, DPR Record No. 138989) "exhibited decreased mucociliary flow (*i.e.*, a breakdown of potentially protective mechanisms) and cellular alterations indicative of an early stage in a process that could lead to cancer". In addition, workers have frequently respiratory or skin irritation effects below 3 ppm (see p. 46250 regarding references to both rat and human findings).
3. The Final Rule of (1992) was also produced by OSHA. This document (29 CFR Part 1910, "Occupational exposure to formaldehyde" [Response to Court remand: final rule], dated May 27, 1992, pp. 22290-22328) further reduced the permissible TWA 8-hr exposure level to 0.75 ppm. This regulation reflected union and consumer interest groups' concerns that the 1987 levels were not sufficiently protective, considering both cancer risk and irritant effects. Aldous, 12/16/96.

METABOLISM

1032-029 133134 Mills, S.C. et al., "Metabolism of [^{14}C]formaldehyde when fed to ruminants as an aldehyde-casein-oil complex". Aust. J. Biol. Sci. 25:807-816 (1972). No worksheet is provided, since ruminant metabolism may be vastly different from humans. Abstract states that when formaldehyde was fed to cows, 60-80% was metabolized to carbon dioxide and methane, 11-27% was excreted in feces, and 5-6% was excreted in urine. Aldous, 3/18/96.

1032-029 133142 Malorny, G., N. Rietbrock and M. Schneider, "Die Oxydation des Formaldehyds zu Ameisensäure im Blut, ein Beitrag zum Stoffwechsel des Formaldehyds", Naunyn-Schmidebergs Arch. exp. Path. u. Pharmakol. 250:419-436 (1965). Mongrel dogs were dosed iv or orally with formaldehyde, and blood was analyzed for formaldehyde and formic acid. An oral dose of 70 mg/kg formaldehyde led to a rapid increase in circulating formic acid (peak at 2 hr of about 13 mg%), and a corresponding drop in blood pH from about 7.45 predose to a minimum of about 7.3. There was a measurable peak in RBC formaldehyde (about 1 mg% at 15 min after dosing), followed by relatively constant, much lower

formaldehyde RBC levels. Infusion (iv) similarly led to rapid increases in circulating formic acid levels. Formaldehyde in RBC's was several-fold higher than in plasma during infusion. As with oral dosing, RBC formaldehyde levels were measurable, but much lower than that of circulating formic acid. Formic acid at time 0 was about 27 mg% in blood, with a drop to about 2 mg% by 6 hr. Data do not warrant a worksheet, but report is useful in showing the rapid oxidation from formaldehyde to formic acid. Aldous, 3/19/96.

CHEMICAL CHARACTERISTICS OF FORMALDEHYDE AND PARAFORMALDEHYDE

1032-054 151306, 151308, 151309, 151310, 151311, and 151312 (data describing relationship of formaldehyde monomer and polymeric forms submitted for upgrades of chronic and teratology studies). Cover letter date: 11/26/96. (Literature excerpts were given Sunkist Reference Nos. 789, 021, and 698). Page 3 of the cover letter notes that paraformaldehyde is a linear polymer of formaldehyde, which rapidly depolymerizes into the monomer in water; that at the low concentrations used in animal studies, paraformaldehyde rapidly transforms into formaldehyde; and that the resulting formaldehyde is stable under laboratory conditions. The literature data indicate remarkable influence of pH on the rate of dissolution of paraformaldehyde, with the slowest dissolution occurring at about pH 4 (Ref. 789, pp. 009-010). At concentrations in which paraformaldehyde is not dissolved, solution temperature and standing time remarkably affect eventual solubility of the resultant polymerized material on subsequent heating (Ref. 789, p. 027). The 3 references tend to focus on characteristics of comparatively high concentrations of formaldehyde and associated polymers. An empirical equation for estimating the amount of monomer in solution suggests that relatively low concentrations of formaldehyde (typical of drinking water studies) would be nearly 100% solubilized (Ref. No. 021, p. 002). The extent to which dilute dosing dilutions of formaldehyde are oxidized to formic acid, reduced to methanol, condensed to hydroxy aldehydes, or otherwise subjected to covalent bond alterations via metal catalysis or influenced by pH or bacterial degradation or other influences is not clear (Ref. No. 021, p. 002). This is potentially useful information, but does not substitute for retrospective analysis of dosing solutions under conditions of the bioassays. Aldous, 12/17/96.